HYPO-ADRENALISM AND PELLAGRA

THE ROLE OF VITAMIN DEFICIENCY

BY

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Pellagra is commonly regarded as a disease due to deficiency of vitamin B₂, and the impression prevails that, confronted with this illness, we need merely add yeast to the patient's diet in order to effect a cure. That vitamin deficiency plays a very important part is indisputable; in this paper, however, it is suggested that B₂ avitaminosis is not the sole causative factor. Moreover, Parfitt (1936) recently reported that after large doses of yeast a patient suffering from pellagra improved dramatically, only to collapse suddenly and die some days later. Pellagrous dermatitis may clear up after vitamin B₂ has been given, but it seems clear that vitamin C may be equally effective (*vide infra*). Again, Biggam and Ghalioungui (1933) reported considerable success with massive doses of iron in an extensive series of cases of pellagra. In a child of 8 years whom I have at present under my care, a dermatitis coming on after exposure to strong sunlight, and very suggestive of pellagra, has cleared up more than once after vitamin B₂, but the patient's general condition, mental and physical, is steadily deteriorating. It ought therefore to be realized, as Muir (1936) says, that further investigation is necessary before we can pronounce as to the relation of vitamin B₂ to pellagra.

Leaving for the present the problem of the exact association of vitamins with pellagra, the undernoted case history is submitted. This shows once again what has been brought forward from time to time during the past thirty-five years, that there exists a close connexion between pellagra and suprarenal hypofunction; and the purpose of this paper is to suggest that the fundamental aetiological factor in pellagra is hypo-adrenalism, avitaminosis acting only as an accessory cause.

Illustrative Case

The patient was a woman of 45, happily married and comfortably off; she had two sons, 18 and 15 years of age. Her husband and children were in good health. She was born in Scotland, and both her parents were of pure Scottish extraction. On December 5, 1935, she was admitted to hospital complaining of weakness, lassitude, anxiety, nervousness, insomnia, anorexia, constipation, abdominal pain, and discomfort, all of six months' duration. She was, however, well nourished, and had been taking a good mixed diet. Her height was 5 ft. 3 in. and her weight 9 st. 3 lb. Investigation failed to disclose any gross physical abnormality; the blood Wassermann reaction was negative.

The tentative diagnosis was one of hypochondriasis, with, however, this important reservation—that there might be present some undefinable endocrine disorder. The reasons for this reservation were as follows: (1) The patient had a history of hyperthyroidism in 1928, from which illness she was supposed to have made a good recovery under medical treatment. (2) Her appearance suggested a peculiar compound of hyperthyroidism and hypothyroidism. (3) She was distinctly Italian-looking, her skin exhibiting a generalized amber pigmentation and her hair being very dark and of silky texture. Suprarenal hypofunction, as a possible cause of her illness, was considered. Nevertheless, as her blood pressure was normal, and as at times she jogged herself out of her ideas of weakness and lassitude, especially when she had visitors at her bedside, and as x-ray examination revealed no suggestive shadows either in the chest or in the suprarenal areas, no confirmatory evidence could then be obtained.

On December 28, twenty-three days after admission, she was allowed to go home. She had taken a well-balanced diet, there had been no evidence of gastro-intestinal upset, and, aided by an occasional grain of luminal, she had slept quite well. She was improved in bodily and mental health.

Two months later she had so far relapsed that she was referred back to hospital from the Public Health Department Out-patient Psychiatric Clinic. Readmitted on March 5, 1936, she again complained of abdominal and anxiety symptoms. Noteworthy points on physical investigation were: blood pressure, 130/80; pulse, 85; menstruation, which had been absent for fifteen months until November, 1935, was now regular, but diminishing in quantity; exophthalmos was present; the face was puffy and the whites of the eyes pearly; the ocular fundi were normal; the skin of the forearms and hands was rough and very cold to the touch; a fractional test meal showed achlorhydria; the deep reflexes were exaggerated; there was a fine tremor of the hands; radiographs of the chest were negative and of the abdomen showed visceroptosis. Two points should be specially noted: (1) with regard to pigmentation, a slight deepening of the generalized amber colour had occurred; (2) the body weight had fallen to 7 st. 10 lb., a loss of 21 lb. in about ten weeks. Mentally, an element of depression had moved well into the foreground, but there was no retardation; and memory, orientation, and perception were normal.

On April 25, 1936, the patient developed an acute tonsillitis (*Streptococcus viridans*); this completely cleared up within a fortnight, with subsequent substantial mental and physical improvement. On June 16 she complained of headache and insomnia, which persisted for over a week. On July 11 she developed marked diarrhoea, which proved extremely difficult to overcome. Bacteriological examination of stools revealed no abnormality. About the middle of August a marked change took place in her mental condition; she became exceedingly dull and depressed. She presented the picture of an acute agitated melancholia, and the power of ideation, previously always well developed, now became notably deficient. She then began to waste, and her weight quickly fell to 6 st. 6 lb.; she felt very weak. A deep-brownish pigmentation appeared symmetrically on the dorsum of the hand and wrist, and a few spots on the neck. The blood pressure fell down to 90 mm. Hg systolic, and diarrhoea returned. A diagnosis of Addison's disease was made, and vigorous treatment was started by the excess sodium chloride method, including large doses of intravenous saline daily. Suprarenal and mixed gland extracts—desiccated suprarenal gland adrenal substance, Parke, Davis and Co., and mixed gland (female) tablets, Evans Sons Lescher and Webb, two tablets of each three times daily—were also given and, generally, all stimulating measures were adopted. Her appetite was poor, but care was taken to see that she received a full, well-balanced diet, with plenty of vitamins. She showed immediate response to these efforts: within five days her systolic blood pressure had gone up to 105 mm. Hg, and by the end of August to 110/65 mm. Her weight, however, continued to fall. Small doses of insulin were given, but she complained of great nausea after the injections. Intensive salt and glandular treatment was continued until September 7. She persistently complained of abdominal discomfort, and diarrhoea proved very intractable. Stools were negative for occult blood, and bacteriological examination revealed nothing of importance; but examination on October 20 showed great increase of streptococcal content, with the presence of *B. pyocyaneus*. This is a frequent terminal finding in debilitated mental patients, and is of no particular significance.

At the beginning of November, it having been observed that Demole (1936) had made out a good case for vitamin C as an augmentor of suprarenal cortical function, a copious quantity of lemon juice was added to the diet. The result was striking; almost at once the pigmentation on the backs of the hands began to clear. But the patient was wasting fast; her weight was now only 5 st. 12 lb., and the blood pressure 105 mm. Hg. Meantime Dr. Stewart, the visiting psychiatrist, had pointed out that the pigmentary changes of the hands suggested pellagra, and on November 17 Dr. McLachlan, the dermato-

logist, confirmed this diagnosis on the following grounds: (1) atrophy of skin on back of hands and on the lower half of the face; (2) distribution of the excess of cutaneous pigment; (3) presence of gastro-enteritis and of mental symptoms; (4) history of attacks of redness of skin of face and hands. The patient had become difficult to feed, but nevertheless was still getting a good general diet. She complained of tingling and crampy pains on the soles of both feet and a feeling of great weakness. By November 20 her blood pressure had fallen to 90 mm. Hg. Blood examination showed a secondary anaemia. Mentally she was less agitated. On November 23, without any warning, she had a rigor and was afterwards in a state of semi-collapse. Recovering from this, she presented for the first time a state of acute confusional insanity. She was utterly incapable of apprehending the nature of her surroundings; she suffered from visual and auditory hallucinations, and showed extreme motor restlessness; her blood pressure had fallen to 68 mm. Hg, and there was a coarse tremor of hands and feet. On November 24 the blood pressure fell to 48 mm. Hg, and death was ushered in with delirium and urgent dyspnoea.

The post-mortem examination was conducted by Dr. Marjorie Gillespie, to whom I am indebted for the following relevant notes. The heart was small; the stomach and intestines showed patchy congestion of the wall, the condition being most marked in the caecum and ascending colon; microscopically the thyroid gland showed hyperplasia passing into hypoplasia; no gross lesion was present in the suprarenal glands. Microscopical examination of the skin by Dr. McLachlan revealed marked hyperkeratosis; excess pigment present in superficial layer of epidermis; slight irregularity and elongation of the rete cones; no atrophy in the sections examined. Collagen fibres in the subepithelial layer had undergone a small degree of hyaline change; some of the papillae showed a certain amount of oedema. No changes of pathological importance were found in the corium. A very slight infiltration of the pars papillaris had occurred. Examination of the skin coincided with the clinical observation that pigmentation was disappearing after giving vitamin C.

Discussion

The first question arising in the present case is whether the diagnosis of Addison's disease was correct or whether the patient suffered primarily from pellagra. That no lesions were found in the suprarenal glands is of no help in arriving at an answer. Disease is a process concerned with living cells, and functional derangement is not necessarily associated with anatomical changes of so gross a character that they are demonstrable even with the aid of the microscope. Especially is this the case when the diseased tissue is obtained at post-mortem examination of the human subject.

Another difficulty arises from the fact that textbook descriptions of the syndromes of suprarenal dysfunction and pellagra show a striking correspondence. In both we find very similar alimentary, nervous, and integumentary symptoms. In the present case, however, whether the true diagnosis was Addison's disease or pellagra, certain features tend to place the primary disorder at the door of the suprarenals—namely: (1) Hypotension, becoming gradually worse. (2) Favourable response to suprarenal therapy. (3) Previous history of endocrine disorder. (4) Generalized pigmentation present for many years before she came under care. (5) The patient's age; and disorder of menstruation. (6) Her death was in the nature of an acute collapse, and this has often been associated with adrenal failure. One need only mention such conditions as toxic diphtheria, malarial collapse, and surgical shock. (7) The histological appearances of the thyroid gland were those associated with hypothyroidism following upon hyperthyroidism. It is suggested that long-standing cortical adrenal hypofunction

may have caused, first, a relatively overacting thyroid ("The cortex is the very antagonist of the thyroid"—Goldzieher, 1929), with a final adreno-thyroid exhaustion.

Furthermore, it is interesting to note that although the patient finally developed pellagra, (i) there was no dietetic (either protein or vitamin) deficiency of intake; (ii) on the same diet as the forty other patients in the ward she was the only one to acquire the disease; (iii) being a bed patient she was not more exposed to the sun or other trauma than any of the others; (iv) no infective condition was present. Here, therefore, is a case of hypo-adrenalism terminating in "pellagra" with no factor either of deficient nutritional intake or of infection to account for such a development.

Even if this adrenal-pellagra combination had never been previously noted, the case here described would have been of interest because of the uncertainty surrounding the aetiology of pellagra. Since, however, so many observers have called attention to this phenomenon there is evidently here a fruitful field for exploration.

RELATION BETWEEN ADDISON'S DISEASE AND PELLAGRA

Simpson (1935), when describing two cases of secondary pellagra, called attention to the connexion between Addison's disease and pellagra, and concluded that a definite relation exists. He also quoted from Harris (1919) eight cases of Addison's disease reported by Finotti and Tedeschi (1902) which had terminated as pellagra and which had shown severe post-mortem adrenal changes, as well as other cases since that time which showed pellagra supervening upon Addison's disease. Parfitt (1936) does not mention the association between Addison's disease and pellagra, but the two cases described by him as pellagra could also be described as typical clinical examples of hypo-adrenalism, and Watson (1922), commenting on fourteen cases diagnosed as pellagra at Rainhill Asylum, made the following significant observations: (1) The age grouping was between 40 and 50 years; (2) the course of the disease measured only in weeks (except in the two youngest of the series); (3) the diet of the patients had been more varied and more generous than usual.

Examining more closely this association between the symptoms of hypo-adrenalism and pellagra, it will at once be conceded that no substantial difference exists either in the alimentary or pigmentary phenomena (Rowntree, 1925; Goldzieher, 1929a, 1929b). Hypotension, however, demands careful scrutiny. Here we appear to be confronted with an exclusively Addisonian sign, yet a careful search through the literature reveals that the question of blood pressure in pellagra is scarcely ever mentioned. Stannus and Gibson (1934) reviewed all the cases diagnosed as pellagra in Britain up to 1934, but no reference is made to blood pressure. Parfitt (1936) and Simpson (1935) each describe two cases in which the blood pressure was low. *It is at least open to question whether in pellagra the arterial tension could possibly be maintained at a normal level in face of the array of debilitating symptoms.* At post-mortem examination the heart in pellagra is found to be small, just as it is in Addison's disease. Is it not probable that in the combination of low metabolism and diarrhoea (both common to Addison's disease and pellagra) there lies the common explanation of diminished tension and small size of heart?

SEX INCIDENCE

Combined figures of sex incidence in Addison's disease and pellagra show a preponderance of females over males. If, as seems at least suggestive, suprarenal hypofunction

is the common antecedent of both clinical syndromes, this is what one would expect, since fundamental glandular weaknesses are more likely to be exposed in females. Hutton and Steinberg (1936), commenting upon 176 clinic patients suffering from definite endocrinopathy, give the sex incidence as 146 female and thirty male. Stannus and Gibson (1934) give the sex incidence of 131 British cases diagnosed as pellagra from 1912 to 1931 as 111 female and twenty male—a remarkable similarity in ratio. It is difficult to imagine such a gross sex disparity arising entirely from a difference in vitamin intake. Assuming, however, a sex equality of vitamin intake and absorption, women might conceivably suffer more readily than men if certain vitamins were found to be essential elements in the maintenance of suprarenal and other endocrine functioning. Average vitamin absorption might then prove relatively insufficient because of increased endocrine demands, particularly at times of physiological stress. The large proportion of female cases of so-called pellagra occurring at the menopause is significant. In other words, one of perhaps many factors which bring to light endocrine discord and precipitate an apparent unilateral endocrinopathy may well be insufficient intake or absorption of certain vitamins, and especially so at the climacteric. Again, what appears to be a disease purely of vitamin insufficiency may, moreover, be the expression of a latent endocrine abnormality. Does any evidence exist of such an association as is here implied between vitamins and the suprarenal glands? The undernoted observations regarding vitamin C are of interest.

(i) The suprarenals are known to be particularly rich in ascorbic acid. (ii) Demole (1936), employing the test for vitamin C subnutrition devised by Harris and Ray (1935), found that the body of the Addisonian patient is impoverished of vitamin C. (iii) Wilkinson and Ashford (1936) describe three patients suffering from Addison's disease, all showing vitamin C subnutrition, the degree of subnutrition paralleling the severity of the illness. (iv) Demole (*loc cit.*) quoted the following additional points of interest: (a) Striking demonstrations by Thaddea have proved that resistance to experimental infection in adrenalectomized animals requires vitamin C as well as cortin. Thaddea concludes that if vitamin C does not augment production of cortin its presence is useful for the proper functioning of the suprarenal cortex, probably acting as a powerful augments of the action of cortin; (b) Szent-György has shown that vitamin C diminishes Addisonian pigmentation, and (c) to several Continental preparations of suprarenal extract ascorbic acid is now added. (v) Many observers have recorded diminution of pathological pigmentation with lemon juice; and the case described in this paper is yet another example. (vi) Lockwood and Hartman (1933) mention delay of onset of symptoms of B and C avitaminosis with injections of suprarenal cortical extract.

Although much work remains to be done to establish the precise relations between vitamin C and the suprarenals, the existence of some synergistic association is probable.

SECONDARY PELLAGRA

Since 1916 it has been maintained that there exists a separate clinical entity known as secondary pellagra; this has been defined by Simpson (1935) as "pellagra occurring secondary to an initial gastro-intestinal lesion or disorder, the causation of which is entirely unconnected with pellagra." It is suggested that the grounds for this clinical distinction are inadequate. One may as well describe an Addisonian patient first seen with gastro-intestinal symptoms as a "secondary Addison."

If it were proved that pellagra is merely a manifestation of hypo-adrenalism, and if the need of the suprarenals for

adequate vitamin stimulation were established, a simple explanation would then suffice for the essential nature of both primary and secondary pellagra—namely, that the gastro-intestinal disorder prohibits adequate absorption of the vitamins requisite for suprarenal functioning. Such a thesis is supported by the fact that achlorhydria occurs both in hypo-adrenalism and in pellagra. Thus the aetiology as well as the symptomatology of functional hypo-adrenalism and pellagra could be brought under a common heading. In other words, the cause of pellagra could be described as hypo-adrenalism precipitated by avitaminosis.

It is hoped that the points raised in this paper may result in a closer scrutiny of all suspected cases with a view to furthering the knowledge of the hypo-adrenal-pellagra association. Certainly in cases of so-called pellagra there should be a routine investigation made of the blood pressure, of the gastric juice, of the ascorbic acid excretion, and of the endocrine as well as of the dietetic factors.

Treatment

Until the question of hypo-adrenal-pellagra relations is definitely determined the suggestion is advanced that treatment of the patient should be directed on the following lines. (1) *Diet* should be generous and varied. (2) *Vitamin therapy*: Large doses of vitamins A, B, C, and D should be included in the diet; lemon juice, egg-white, and cod-liver oil daily will probably cover all requirements. (3) *Cortin*: A commencing dose of 10 c.cm. suprarenal cortical extract, intramuscularly, daily until the condition is stabilized. (4) *Sodium chloride*: 15 grammes a day intravenously and excess salt in the diet. (5) *Acid HCl and pepsin* with all meals. (6) *Pil. Blaud.* (7) *Adrenaline*: Small subcutaneous doses frequently until stabilization.

Summary

1. The specific value of vitamin B₂ in pellagra is called in question.
2. A case is described showing "pellagra" as a terminal manifestation of hypo-adrenalism.
3. Attention is called to a probable relation existing between vitamin C and the suprarenal cortex.
4. Many of the features characteristic of functional hypo-adrenalism, pellagra, and secondary pellagra strongly indicate that these conditions have aetiological factors in common.
5. It is suggested that two essential points in the aetiology of pellagra are: (a) primary hypo-adrenalism; and (b) inadequate vitamin augmentation of adrenal functioning.

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